Decision Memo for Levocarnitine for End Stage Renal Disease (CAG-00077N)

Decision Summary

This decision memorandum announces our intention to issue a national coverage determination for the use of levocarnitine in ESRD patients. Intravenous levocarnitine will only be covered in ESRD patients who have been on dialysis for a minimum of three months for one of the following indications:

Patients must have documented carnitine deficiency, as noted by a pre-dialysis (trough) plasma free carnitine level < 40 micromol/L, along with signs and symptoms of:

1. Erythropoietin-resistant anemia (persistent hematocrit < 30% with treatment) that has not responded to standard eythropoietin dosage with iron replacement, and for which other causes have been investigated and adequately treated; or

2. Hypotension on hemodialysis that requires intervention and is unresponsive to all usual management measures (e.g., fluid management) and interferes with dialysis. Such episodes of hypotension must have occurred during at least 2 dialysis treatments in a 30-day period.

Continued use of levocarnitine will not be covered if improvement has not been demonstrated within 6 months of initiation of treatment. Most of the studies reviewed that reported a positive result found a benefit with levocarnitine within six months or less of treatment.

All other indications for levocarnitine are noncovered in the ESRD population.

For a patient currently receiving intravenous levocarnitine, Medicare will cover continued treatment if:

1.

Levocarnitine has been administered to treat an indication covered under the national policy described above; and

2.

The patient's medical record documents a pre-dialysis (trough) plasma free carnitine level < 40 micromol/L prior to the initiation of therapy; or

3.

The treating physician certifies that in his/her judgment, if treatment with levocarnitine is discontinued, the patient's pre-dialysis carnitine level would fall below 40 micromol/L and the patient would become symptomatic from erythropoietin-resistant anemia or intradialytic hypotension.

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Decision Memo

TO: Administrative File CAG-00077N
Levocarnitine Injection

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RE: Coverage Decision Memorandum for Intravenous Levocarnitine in End-Stage Renal Disease

DATE: July 22, 2002

This memorandum serves four purposes: (1) provides clinical background on levocarnitine and carnitine deficiency, focusing on carnitine deficiency in end-stage renal disease (ESRD) patients who become symptomatic while carnitine deficient; (2) reviews the history of Medicare's coverage policies and provides a timeline of recent activities; (3) presents and analyzes the relevant scientific and clinical literature on the use of levocarnitine in ESRD patients; and (4) delineates the reason for announcing our intent to issue a national coverage decision for specific clinical uses of levocarnitine in ESRD patients.

Clinical Background

Carnitine (3-hydroxy-4-trimethylaminobutyric acid) is a naturally occurring substance that functions in the transport of long chain fatty acids across mitochondrial membranes resulting in the production of ATP (adenosine 5'-triphosphate), which the body uses as a source of energy. It is ingested in foods of animal origin. Carnitine is also synthesized in the human liver and kidney. Deficiency can occur due to a congenital defect in synthesis or utilization, or from dialysis. Congenital defects are rare. They produce a decrease in intracellular carnitine that impairs fatty acid oxidation. Clinically, patients are typically normal at birth, but then fail to thrive, develop recurrent respiratory infections, and recurrent attacks of hypoglycemia. Investigators have hypothesized that possible signs and symptoms that may be associated with carnitine deficiency in ESRD patients include anemia, intra and interdialytic complications or symptoms (such as hypotension), cardiac dysfunction, impaired exercise capacity and muscle strength, and impaired lipid metabolism. These signs and symptoms are discussed in greater detail below.

The causes of deficiency in hemodialysis patients include dialytic loss, reduced renal synthesis, and reduced dietary intake. Total carnitine levels have been reported to decrease as much as 70% with a single hemodialysis treatment. Typically, carnitine levels begin to rebound immediately after dialysis; few patients develop biochemical or clinical evidence of carnitine deficiency.

In clinical practice, plasma levels are commonly used to diagnose carnitine deficiency; however, these values do not always reflect the tissue carnitine concentrations or total body carnitine levels. Plasma free carnitine refers to the non-acylated forms of levocarnitine, and represents about 80% of the total carnitine. The remaining 20% is bound to short, medium, and long-chain acylgroups. In healthy adults, the plasma free carnitine is approximately 40-50 micromol/L, total carnitine is approximately 50-60 microM, and the ratio of acylcarnitine to free carnitine is < 0.4

Food and Drug Administration (FDA) Approval

The Food and Drug Administration (FDA) first approved levocarnitine in 1985 for primary carnitine deficiency. In 1992, the FDA approved the intravenous (IV) and oral forms for the acute and chronic treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency.

On December 15, 1999, the FDA approved injectable levocarnitine for the prevention and treatment of carnitine deficiency in patients with end-stage renal disease who are undergoing chronic dialysis. The FDA determined that levocarnitine is effective in maintaining and increasing carnitine serum levels in ESRD patients on dialysis. However, the FDA has not approved levocarnitine as a treatment to improve a clinical sign, symptom or other health outcome associated with levocarnitine deficiency in this patient population, because data to support such a claim was not presented to the agency. The labeling for levocarnitine states that normal plasma free carnitine levels are 40-50 micromol/L. The FDA has indicated, however, that clinical manifestations of carnitine deficiency generally do not occur until levels fall to less than 20% of normal.

History of Medicare Coverage Policies and Timeline of Activities

Presently, no national coverage policies exist on the use of levocarnitine. Therefore, the decision to cover the use of intravenous levocarnitine in ESRD patients has been determined by individual contractors. As a result, there are varying degrees of coverage; some contractors cover carnitine only for inborn errors of metabolism, while others have some coverage for ESRD patients if they meet certain indications. Both the fiscal intermediaries and Sigma-Tau Pharmaceuticals, the manufacturer of the brand name form of levocarnitine, spoke separately to the agency to discuss their interpretations of the data.

Because of the different viewpoints, on April 18, 2001, CMS internally generated a request for a national coverage decision on the use of levocarntine for ESRD patients. The issue was also referred to the Center for Health Plans and Providers (CHPP) for final benefit category determination.[1] The benefit category is an institutional dialysis service/supply under § 1861(s)(2)(F) of the Social Security Act. Our tracking sheet used § 1861(t)(1) as a placeholder until a benefit category had been determined. Section 1861(t)(1) defines “drugs” and “biologicals” but is not a distinct Medicare benefit category. Section 1861(s(2)(F) includes within the scope of Part B services “institutional dialysis services and supplies.” Levocarnitine is generally administered intravenously to ESRD patients following a hemodialysis treatment in an institution that provides dialysis.

May 18, 2001 CMS referred the matter to the Medicare Coverage Advisory Committee (MCAC) /Drugs, Biologics, Therapeutics Panel to allow broad public input and an open debate between all interested parties.

June 20, 2001 MCAC meeting at the Baltimore Convention Center.

October 17, 2001 Recommendations ratified by the MCAC Executive Committee.

November 30, 2001 Minutes from October 17, 2001 of MCAC Executive Committee meeting received by CMS.

General Methodological Principles of Clinical Study Design

There are several generally accepted methodological principles when assessing a clinical trial. For example, we evaluate whether or not general methods of study design have been followed, such as calculating sample size *a priori*, specifying inclusion and exclusion criteria, describing the process for the selection of study participants and the ways in which the consistency of this process was maintained, ensuring comparability of experimental and control groups at baseline to the extent possible, describing baseline characteristics of the participants, randomizing study subjects, masking of patients and investigators to the therapy administered to the extent feasible, describing co-interventions in detail, and performing appropriate statistical analyses, such as statistical tests of differences in baseline characteristics between the comparison groups.

Summary of Evidence

A literature search was conducted using the following terms: “carnitine”, “kidney failure”, “chronic or renal dialysis”, or “dialysis”. Multiple searches resulted in 186 articles: 44 were initially excluded for the following reasons: (1) Non-English (2) Non-human subjects or (3) Acute renal failure. Of the remaining 142 studies, there were 16 randomized clinical trials (RCTs), 51 non-randomized clinical trials, 30 case controls or cohort studies, 22 reviews or editorials, and 23 letters to the editors.

The following *inclusion criteria* were applied to these 142 articles:

- Clinical trials
- Human ESRD subjects
- Minimum of 10 subjects
- Published after 1980
- Clinically relevant outcome measures

Clinically relevant outcome measures included cardiac function, lipid profile, anemia or coagulation profile. Measures needed to correlate to improved health outcomes.

After applying these inclusion criteria, there were 36 articles, including the16 RCTs, 19 non-randomized clinical trials (primarily crossover design), and one case series.

The overall subject population from the 36 studies was approximately 1,100 subjects—this is less than the summation of subjects across all the articles because there are several pairs of articles reporting different outcomes from the same study population. Twenty-four studies investigated intravenous administration of carnitine, 12 studies investigated oral administration, and 4 examined carnitine in the dialysate solution. These numbers add up to more than 36 because several studies looked at multiple routes of carnitine administration.

The vast majority of the studies examined L-carnitine. There were a small number of investigations of DL-carnitine in the early 1980s. DL-carnitine was reported to cause a myasthenia-like neuromuscular syndrome that appeared to be dose dependent; however, that formulation is no longer used and similar symptoms have not been reported with L-carnitine.

In general, the number of subjects in each study was small. Only 9 of the 36 studies enrolled more than 30 subjects. The study duration varied from as little as four weeks to greater than one year, with a mean follow-up of 23.3 weeks. A majority of these studies utilized double blinded methodology with a placebo control group.

The studies reported on a wide variety of outcome measures. This variety of outcomes makes it difficult to discuss aggregate results across all the articles. As a result, the studies were grouped into the following five general categories based on specific outcome measures that are similar to categories used in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) literature review:

- Anemia (changes in hemoglobin, hematocrit and recombinant human erythropoietin requirements).
- Intra and interdialytic complications or symptoms (interdialytic hypotension, muscle cramps, fatigue, asthenia, as measures of general well being or quality of life[2]).
- Cardiac function (presence of arrhythmia and quantification of ejection fraction).
- Exercise capacity and muscle strength (objective measurements of exercise muscle strength and changes in muscle fiber morphology by histologic examination of biopsy tissues).
- Lipid metabolism (changes in triglycerides, cholesterol, HDL, LDL).

Studies that Assessed the Carnitine Effects on Anemia

Author	Year	N	Route	Iron Status	Hgb	Hct	RHuEPO Requirements
Bellinghieri (cross over double blind trial)	1983	14	PO	No	NR	Incr 27/25 to 31*	NR

Author	Year	N	Route	Iron Status	Hgb	Hct	RHuEPO Requirements
Brass (RCT)	2001	183	IV	No	No change	No change	NR
Caruso Ø (RCT)	1998	27	IV	Baseline	NR	No change	PGrp incrat Ph-3 *
subgroup		age>65 22				PGrp Hct lower at Ph-3 * RxGrp no change	RxGrp decr at Ph-2 RxGrp incr at Ph-3 * PGrp incr at Ph-2 & 3 *
Kletzmayr Ø (RCT)	1999	40	IV	Yes (Rx)	No change	NR	Decr (172 vs 152 U/kg/wk) (NS) ERI decr * (8/19 “responders”)
LaboniaØ (RCT)	1995	24	IV	Yes	NR	PGrp decr (29.5 vs 27.9) * RxGrp no change	PGrp no change RxGrp decr 38% *
Matsumura Ø (case series)	1996	26	-	No	NR	NR	rHuEPO and RBC hemolysis indices correlated with total and free carnitine levels *
Nilsson-Ehle (RCT)	1985	28	IV	No	No change	NR	NR
Semeniuk (RCT)	2000	16	IV	Yes	No change	NR	No change

Author	Year	N	Route	Iron Status	Hgb	Hct	RHuEPO Requirements
Thomas (RCT)	1999	17	IV	Yes	No change	No change	NR
Trovato Ø (RCT)	1982	26	PO	Yes	Incr (7 vs 12.2) *	Incr (25 vs 37)	NR
Vacha (cross over double blind trial)	1983	29	IV/D	No	NR	Incr (24.2 vs 26.6) *	NR
Summary			**8 IV 2 PO 1 D**		**1 Increase 5 No change 6 NR**	**5 Increase (or decrease in PGrp) 3 No change 4 NR**	**3 Decrease (or increase in PGrp) 1 No change 6 NR**

Ø = Anemia was a primary focus of study
IV = intravenous
PO = oral
D = dialysate
NR = Not reported
* = significant p-value (<0.05)
Ph- = Phase
PGrp = Placebo group
RxGrp = Active treatment group
Rx = Active treatment

A total of eleven studies were reviewed, eight of which were randomized controlled trials (RCTs), concerning the effect of carnitine on anemia parameters. In five of the articles anemia was a primary focus, in the others it was a secondary outcome. All but two studies included less than 30 patients. Eight studies involved IV carnitine, two involved oral carnitine, and one delivered carnitine via dialysate. Since iron status is an important factor in the management of anemia in ESRD patients, studies were reviewed to determine if measures of iron status were incorporated. Six did, including one study that used active iron therapy in all subjects, and five did not.

Of the six studies that reported on hemoglobin (Hgb), five showed no change after carnitine therapy and one showed a significant increase. Of the seven studies reporting on hematocrit (Hct), three reported an increase in hematocrit after carnitine therapy, two reported no change in the active carnitine group but a decreased hematocrit in the placebo control group, and three showed no change with either no control group or no change in the control group.

For example, Trovato (1982) randomized 26 patients to 1.6 gm carnitine orally for 12 months or placebo. Outcome measures included Hgb, Hct, Red cell count, MCV, reticulocyte and transferrin. The average age of patients was 47.5 years, and groups were comparable at baseline. At the end of the study, the experimental group demonstrated a Hgb increase over 50% from a baseline of 7 to 12.25 ($p<0.01$). Hct also increased nearly 50% as well from a mean of 25 to 37 ($p<0.001$). No significant changes occurred in the control group, although there was a trend to decrease in Hgb. Of note, the improvement started at 3 months with further increases in successive months. There was a low drop out with 2 patients being excluded from the control group since they required a blood transfusion. It does not appear that an intent-to-treat analysis was performed.

Bellingheri (1983) utilized a crossover double-blind design to evaluate changes in Hct with the use of carnitine. Patients were divided into two groups: Group 1- Seven patients received one gram carnitine orally twice a day for two months, and then placebo for two months; Group 2 – Seven patients received placebo for two months, and then switched to oral carnitine for two months. Patients had a mean age of 49 years, and had been on dialysis for an average of 23 months. At the end of the study, Hct showed a significant increase (25 to 31) with the use of carnitine in both groups ($p<0.05$). There were no significant changes in other hematological parameters such as red and white cell counts.

Vacha (1983) enrolled 29 patients in a crossover study utilizing levocarnitine given intravenously post-dialysis for 120 days, then placebo for 120 days. The study's main objective was to examine the effect of carnitine on hypertriglyceridemia; however, they also measured Hct. The average age of patients was 49 years, and the groups were comparable at baseline. At the end of the study, Hct increased in all 29 patients, from an initial average of 24.2 to a final average of 26.6 ($p<0.001$). The clinical significance of this change in Hct is unclear.

Erythropoietin is produced primarily by the human kidney and is an important hormone in the production of red blood cells. ESRD patients develop anemia in part due to reduced production of erythropoietin by the kidneys. Recombinant human erythropoietin can be an effective treatment of severe anemia in some patients with ESRD. Five of the 11 studies reported on erythropoietin requirements in ESRD patients with anemia. Several studies discussed erythropoietin-resistant anemia (which was defined in some of the studies as persistent Hgb < 12 for men, Hgb < 11 for women with treatment). Three trials showed a decrease in erythropoietin requirements after carnitine therapy, one showed no change in the carnitine group but an increase in erythropoietin requirements in the control group, and one showed no change overall.

For example, Caruso (1998) randomized 31 patients to six months IV carnitine therapy or placebo. The mean age was > 65 years, and other than an overrepresentation of males in the treatment group, the groups were comparable at baseline. After six months, both groups were followed for three months without any intervention for a total of nine months. Overall, there was no statistically significant change in hematocrit in either group at phase two or the end of the six-month intervention, or at phase three, the end of the follow-up. When a subgroup analysis was performed on subjects older than 65, which was the majority of the study population, comprising 22 patients, the placebo group had a lower hematocrit at the end of the follow-up at month nine, while the carnitine therapy group had no significant change. Three patients did drop out and it is not clear if an intent-to-treat analysis (wherein all data from all patients, regardless of whether they completed the study, are included in the analysis) was performed. An intent-to-treat analysis can reduce the likelihood of a misleading interpretation of the results that can occur if the experience of all patients is not taken into account. Of note, in the subgroup analysis, patients over the age of 65 in the carnitine group did have lower erythropoietin requirements after six months, and that requirement rose again significantly after three months of not receiving carnitine.

Kletzmayr (1999) randomized 40 patients to either IV levocarnitine or placebo for 8 months. Groups were comparable at baseline. At the end of the study, the carnitine group had a nonsignificant decrease in erythropoietin requirements. Another measure, the erythropoietin resistance index, (a calculated measure - U/kg/week/g of hemoglobin, which is the weekly erythropoietin dose per gram of hemoglobin achieved with that dose), decreased significantly in the carnitine treated group. The erythropoietin requirement decreased in eight of 19 treated subjects. This study was conducted at a single center, with several patients lost to followup. It does not appear an intent-to-treat analysis was performed. The authors did not provide precise characteristics of the responders.

Labonia (1995) randomized 24 patients to receive either IV carnitine or placebo in a six-month trial. Groups were comparable at baseline except for age; patients in the control group were older 62.5 years versus 41.8 years in the treatment group. At the conclusion of the study, subjects receiving carnitine had a 38 percent reduction in erythropoietin dose, measured in terms of units per kilogram per week. Control subjects had no reduction. The authors note that this reduction in the carnitine group was powered by seven of 13 patients who responded, compared to six who did not respond, a differential effect of carnitine therapy similar to Kletzmayer. It is unclear if differences in age could account for the disparate effects seen between groups.

Studies that Assessed Carnitine Effects on Inter- and Intradialytic Complications and Patient Well-Being

Author	Year	N	Route	Measured Parameter(s)	Results
Ahmad Ø (RCT)	1990	82	IV	Global clinical status Intradialytic hypotension Intradialytic muscle cramps Asthenia	PGrp: 8/44 patients improved; RxGrp: 19/38 patients improved * Reduction in RxGrp; no reduction in PGrp * Reduction in RxGrp; no reduction in PGrp * Reduction in both RxGrp and PGrp * Reduction in hypotensive episodes in RxGrp (P<0.02)
Bellinghieri Ø	1983	14	PO	Asthenia and muscle cramps	Group 1 (Rx then placebo): Reduction in symptoms during Rx *

Author	Year	N	Route	Measured Parameter(s)	Results
(cross-over double blind trial)					Group 2 (placebo then Rx): Reduction in symptoms during Rx *
Brass Ø (RCT)	2001	183	IV	KDQ QOL questionnaire	Total score:no change Physical symptoms:no change Fatigue:improvement (RxGrp compared to PGrp) * Depression:no change Interpersonal relations:no change Frustration:no change
Casciani Ø (cross over double blind trial)	1982	18	PO	Rating scale based on patient interview by physician	During Rx, patients reported: Decr in asthenia, cramps, intradialytic hypotension, and dyspnea * No change in 6 other symptoms parameters (appetite, pain, nausea, etc.)
Fagher (RCT)	1985	28	IV	Rating scale based on patient interview	No change in any of nine variables in either RxGrp or PGrp (included fatigue, paresthesias, cramps, appetite, general condition, etc.)
Fujita (pre/post)	1989	18	PO	hypotension	Reduction of frequency of hypotension
Sakurauchi Ø (RCT)	1998	51: 30 Sx 21 ASx	PO: In 30 Sx patients only	Correlation of carnitine levels in Sx compared to ASx groups	Sx patients had lower free carnitine and higher acyl:free carnitine ratios compared to ASx patients (24.4 vs 28.2; 0.84 vs 0.64) *
				Rating scale based on patient interview by physician	Sx patients treated with PO carnitine had a mean score improvement of 1.0 to 1.25 for weakness, fatigue, and cramps * (no comparison to controls)

Author	Year	N	Route	Measured Parameter(s)	Results
Semeniuk Ø (cross over double blind trial)	2000	16	IV	KDQ QOL questionnaire	No change in any parameter during Rx phase compared to placebo phase
Sloan Ø (RCT)	1998	101 a)RCT b)cross	PO	Health-related QOL assessed by the MOS SF -36 form	RxGrp had improvements in physical functioning and general health at 1.5 months; these effects worsened significantly by 6 months compared to PGrp * Subjects staying on carnitine beyond 3 months had a negative perception of general health at 4.5 months *
Thomas (RCT)	1999	17	IV	Cramps, angina, pruritis and general well-being (visual analog scale)	No change
Summary			5 IV 5 PO		7 studies had at positive results for at least one outcome 3 studies had no evidence of effect

Ø = Symptoms were a primary focus of study
IV = intravenous
PO = oral
D = dialysate
NR = Not reported
* = significant p-value (<0.05)
NS = not significant
Ph- = Phase
PGrp = Placebo group
RxGrp = Active treatment group
Rx = Active treatment
Sx = symptomatic
Asx = asymptomatic

The outcome measures used to assess inter and intradialytic complications and patient well-being varied across studies. Generally, these were intradialytic hypotension, muscle cramps, fatigue, asthenia, and quality of life measurements.

Three studies examined the effect of carnitine on intradialytic hypotension (significant drops in blood pressure during dialysis that require a corrective action). Intradialytic hypotension can disrupt dialysis and lead to shock due to low blood pressure in some patients.

Ahmad (1990) administered levocarnitine intravenously to 38 patients over six months in a double-blind, placebo-controlled RCT. Various outcomes were studied, including hypotension. Hypotension was defined as a drop in blood pressure necessitating a corrective action, such as reduction in blood flow or negative pressure or administration of saline or other medication. By the end of the study, the number of patients experiencing hypotensive episodes declined from 44% to 18% in the carnitine group ($p<0.02$), whereas there was no significant change in hypotensive episodes in the control group.[3]

Casciani (1982) enrolled 18 patients in a double-blind crossover study to examine the effect of carnitine on asthenia, cramps, dyspnea, and hypotension. Ages ranged from 20-45 years, and groups were comparable at baseline. Patients were randomized to either: Group 1 received carnitine for 60 days, then a 10 day washout, and then placebo for 60 days; or Group 2 received the reverse order. Intradialytic hypotension was defined as systemic arterial pressure < 90. Frequency was also examined, noting whether hypotension occurred every 10 dialyses, every 5 dialyses, or at each dialysis. At the conclusion of the study, the group receiving levocarnitine showed a statistically significant decrease in episodes of hypotension ($p<0.01$); Group 1 actually showed an increase in hypotensive episodes when carnitine was discontinued ($p<0.001$).

Fujita (1989) studied 18 dialysis patients in a pre/post trial, who had repeated episodes of hypotension (more than 4 episodes of dialysis-induced hypotension in a 4-week period). Patients were given 1200 mg of oral levocarnitine for 12 weeks. Baseline characteristics of both control and experimental groups were similar. By 8 weeks, the mean arterial pressure had risen for the experimental group, while there was no change in the control group. In addition, there was a statistically significant reduction in the frequency of hypotensive episodes ($p<0.05$).

As to other outcomes, the studies used various measures and reported conflicting results. Some also had important methodological flaws. Five studies reported a positive effect or improvement in at least one outcome after carnitine therapy, three studies had no evidence of effect, and one study had both positive early and negative late effects. Of the five IV studies, two were positive and three were negative. Of the oral studies, three were positive and one had both positive and negative effects.

Sloan (1998) is an example of a trial that reported both positive and negative effects. A large number of subjects were enrolled in what was a compilation of two studies. One was a randomized control trial; the other was a double-blind crossover trial. Mean age was 52 years and groups were comparable at baseline. Patients were randomized to one of two groups: A. 1 gm oral carnitine or placebo for 6 months; or B. 3 months placebo followed by 3 months carnitine, or 3 months carnitine followed by 3 months placebo. Quality of life was measured by a standard SF-36 tool. In both the randomized control trial and in the combination of the two trials, oral carnitine had initial positive effect on physical function and general health but that after a four to six-month period, there was a greater decline in the carnitine treated group compared to the subjects on placebo. This finding is counter to the author's hypothesis, and an adequate explanation for these results is not provided. Moreover, there were no changes in intradialytic symptoms.

Brass (2001) used within group and between group comparisons. The authors enrolled 183 subjects in two separate trials of 24 weeks duration: one a randomized control trial comparing 20 milligrams per kilogram IV and a dose finding study, or dose application study, randomizing patients to receive 10, 20 and 40 milligrams per kilogram or placebo. Quality of life was measured by the KDQ, a kidney specific validated quality of life tool. The difference between total quality of life scores at baseline and 24 weeks was 0.44 for the carnitine treated group, and 0.29 for the placebo treated patients. Carnitine-treated patients appeared to have a greater improvement. Of note, those results represent the "within group" comparison baseline to end of study for each group. The "between group" comparison takes into account the changes in the placebo group when evaluating the change in the carnitine group, and this difference was not statistically significant. In addition, it is not clear the clinical significance of the improved scores. The investigators did not appear to account for several dropouts.

Studies that Assessed Carnitine Effects on Cardiac Function

Author	Year	N	Route	Measured parameter (s)	Results
Ahmad (RCT)	1990	82	IV	Arrhythmias	No change in arrhythmias between groups
Fagher (RCT)	1985	28	IV	EF Systolic time intervals LVED Stroke volume Left ventricular posterior wall thickness Left ventricular end -diastolic diameter Left ventricular end-systolic diameter	No change in cardiac tests
Matsumoto (cohort)	2000	9	PO	Chest symptoms (e.g. dyspnea on exertion, palpitations, chest pain) EF LV mass Cardiothoracic ratio (CTR)	Improvement in 11/13 symptoms in all patients CTR: 56.4 to 53.6 p<0.05 EF 44.9 to 53.8 p< 0.05 LV mass reduced by 12.3% (p< 0.05)

Author	Year	N	Route	Measured parameter (s)	Results
Suzuki (cohort)	1982	17	PO	Arrhythmias	>90 % reduction in premature beats
Trovato (cohort)	1998	60	IV/PO	LVED Cardiac output EF	Experimental group showed decrease in LVED from 79.88 to 72.66 (p< 0.05) Increase in cardiac output from 2.59 to 3.32 Increase in EF from 60 to 65 (p< 0.05)
Van Es (cohort)	1992	56	IV	EF	EF all groups: 42.4 to 48.6 (p<0.05) symptomatic: 30.4 to 41.7 (p<0.05) asymptomatic: 51.8 to 56.7

There were six studies of cardiac function, which focused on either changes in ejection fraction/symptoms of congestive heart failure (CHF) or frequency of arrhythmias.

Ejection fraction was measured in four studies.

Fagher (1985) performed a six-week randomized controlled trial in 28 subjects using echocardiography to evaluate ejection fraction and other cardiac parameters (e.g. left ventricular end diastolic (LVED) diameter, systolic time intervals). The mean age was 45 years and groups were comparable at baseline. Average ejection fraction (EF) was 62%, and patients did not have signs of heart failure. Patients were given IV carnitine or placebo for 6 weeks. Using between group statistical comparisons, there was no difference in any parameter at the conclusion of the study.

Trovato (1998) studied 60 patients to evaluate the effect of long-term levocarnitine supplementation on nutritional state of patients in maintenance dialysis. All patients before and at the end of the study were in stable cardiac condition. According to a graph in the article, all patients had an EF around 60 throughout the study. Patient assignment to the treatment group or to the control group was not randomized. Instead, the decision to treat a patient (and, thus, group assignment) “was related to the personal decision of the physician that directly had the group responsibility.” The experimental group was treated with levocarnitine (1 gm IV at dialysis sessions, and 1 gm orally during interdialysis days) for three years or more. The control group was never treated with levocarnitine. Patients were sex and age-matched, and did not have acute/chronic liver disease, chronic infectious diseases and malignancy. At the end of the study, the carnitine-treated group showed a slight, but statistically significant, increase in ejection fraction, and a decrease in left ventricular end diastolic volume in comparison to baseline values. The control group did not demonstrate a statistically significant change. Significant differences in left ventricular dimension and in cardiac output were not observed throughout the study either within each group or between the two groups.

Van Es (1992) enrolled 56 patients in a pre/post cohort trial, divided into symptomatic and asymptomatic patients depending on whether or not they were experiencing hypotensive episodes during dialysis. Each subject received IV carnitine for three months and then had ejection fractions measured first at baseline, and then at three months by gated pool nuclear imaging. The symptomatic patients had a baseline EF of 30.4 % while the asymptomatic group had EF of 51.8%. At the end of the study, there was a mean increase in all patients from 42.4 to 48.6 ($p< 0.05$). This increase was a result of the increase in the symptomatic group, which showed an increase in EF from 30.4 to 41.7, a 37% improvement ($p<0.02$). The asymptomatic group also showed an increase, from 51.8 to 56.7, but this was not statistically significant. Three patients were lost to follow-up. As with all pre/post trials, the lack of a true control makes it difficult to assess the cause of improvements.

Matsumoto (2000) examined the effects of levocarnitine on cardiac morbidity. Nine patients were enrolled; all had chest symptoms, left ventricular hypertrophy, and reduced left ventricular ejection fraction (LVEF) by echocardiography (average 44.9%). Patients were given carnitine daily for 6 months. CHF symptomatology was evaluated by physician interview; LVEF was measured by gated pool scintigraphy, and MRI was used to measure left ventricular mass. At the conclusion of the study, the use of carnitine improved 11 of 13 symptoms measured in all patients (e.g. dyspnea on exertion, palpitation, chest pain). Cardiothoracic ratio, a measure used to examine heart size, showed a statistically significant reduction in size, post-treatment, from 56.4 to 53.6 ($p=0.042$) while LVEF showed a statistically significant increase from 44.9 to 53.8 ($p<0.005$).[4] Left ventricular mass, in general, showed a reduction of 12.3% ($p<0.05$). As with all pre/post trials, the lack of a true control makes it difficult to assess the cause of improvements.

Two studies evaluated frequency of arrhythmias.

Ahmad (1990) utilized a randomized controlled trial of 82 subjects to examine arrhythmias during dialysis. Overall, there was no decrease in arrhythmias in the carnitine group compared to the placebo group. Both groups had few subjects with arrhythmias at baseline; as a result, the study may have been underpowered to detect a difference, although the authors did not provide any actual numbers for this variable.

Suzuki (1982) performed a pre/post study looking at arrhythmias in seventeen subjects with premature beats, both ventricular and supraventricular or other ST-T abnormalities, during dialysis. Mean age was 52 years. All subjects took 2 gm carnitine orally for eight weeks. The authors showed a significant reduction in the number of premature beats (> 90% reduction) both at four and eight weeks compared to the baseline value ($p<0.05$). This study design did not follow an untreated group of patients with baseline arrhythmias, which makes it more difficult to determine causality.

Studies that Assessed Carnitine Effects on Exercise Capacity and Muscle Strength

Author	Year	N	Route	Measured Parameter(s)	Results
Ahmad Ø (RCT)	1990	82	IV	Anthropometrics Max VO_2 Exercise time	Incr in mid-arm muscle mass * (24 patients) RxGrp incr (by 111 ml/kg/min) * (37 patients) No change (37 patients)
Bellinghieri Ø (cross over double blind trial)	1983	14	PO	Muscle fiber morphology	13/14 showed no change in morphology
BrassØ (RCT)	2001	187	IV	Max VO_2	Primary analysis: No change Secondary analysis: Smaller decline in RxGrp (0.05 vs 0.88 ml/kg/min) *
Fagher Ø (RCT)	1985	28	IV	Muscle strength (torque) Dynamic endurance (torque)	No change comparing RxGrp to PGrp No change comparing RxGrp to PGrp
Giovenali Ø (before/after study)	1994	26	IV/PO/D	Muscle strength (isometric)	Incr in strength after Rx in IV and D groups *

Author	Year	N	Route	Measured Parameter(s)	Results
				Muscle morphology	Diameter incr for Type I and Type IIa fibers (all 26 patients considered) * % Atrophic fibers decr for Type I and IIa fibers (all 26 patients considered) *
Rocchi Ø (cohort)	1986	20	IV	Electromyographic activity	Total power incr at months 1 * and 7 * Decr in nerve conduction velocity (NS)
Siami Ø (RCT)	1991	14	IV	Patient self-assessment of muscle strength and activity	Mean score gain of 0.48 in PGrp and 1.3 in RxGrp (NS) 2/7 in PGrp and 4/7 in RxGrp had a score increase of 1 or greater
Spagnoli Ø (cohort)	1990	22	IV	Muscle fiber morphology (based on six patients)	After IV Rx withdrawn there was a significant decr in Type I fiber diameter and hypertrophy score; also an incr in Type 1 fiber atrophy score *
Thomas (RCT)	1999	17	IV	Muscle strength (visual analog scale)	No change

Study Outcome	Number of Studies	Summary Results

Study Outcome	Number of Studies	Summary Results
Anthropometrics	**1**	**1 positive**
Max VO2	**2**	**1 positive; 1 negative (positive after secondary analysis)**
Exercise time	**1**	**1 negative**
Muscle strength	**5**	**2 positive; 3 negative**
Muscle fiber morphology	**3**	**2 positive; 1 negative**

Ø = Exercise/Muscle was a primary focus of study
IV = intravenous
PO = oral
D = dialysate
NR = Not reported
* = significant p-value (<0.05)
NS = not significant
Ph- = Phase
PGrp = Placebo group
RxGrp = Active treatment group
Rx = Active treatment

A variety of outcome measures were utilized to evaluate the effects of carnitine on exercise, muscle strength and muscle morphology. For example, muscle strength was analyzed in five articles, two using objective measures of torque or isometric force, one using objective EMG measures, and two using patient self assessment scores.

Ahmad (1990) looked at numerous measures, including body anthropometric measures, maximal oxygen consumption, as well as exercise time. Baseline symptoms were slightly higher in the carnitine treatment group. At the completion of the study, the authors found a significant increase in mid-arm muscle mass as well as maximal VO_2 in the carnitine group with no change in the placebo group ($p<0.05$). It is unclear as to the clinical significance of these measures; furthermore, anthropometric measurements are difficult to standardize and reproduce. Ahmad also looked at exercise time, a clinically relevant measure, and found no significant differences.

Brass (2001) utilized a multi-center randomized controlled trial to assess exercise capacity. A total of 60 patients were enrolled, and the groups were comparable at baseline. At the completion of the study, there was no statistically significant difference in the primary analysis; however, a secondary analysis using different regression techniques, did show a smaller decline in the max VO_{2max} in the carnitine group compared to the placebo group. Again, it is unclear what is the clinical significance of this measure. Seven patients (six in the treatment group) did withdraw from the study; the authors did use an intent-to-treat analysis.

Five studies examined muscle strength. All had significant methodological flaws. Two were positive and three were negative. The two positive studies used objective measures, isometric force and electromyographic activity; the negative studies included two subjective assessment scales and one objective measure of torque force. Muscle and fiber morphology were measured in three studies; two were positive, showing either an increase in fiber diameter or a decrease in fiber atrophy scores, and one was negative, showing no change.

Studies that Assessed Carnitine Effects on Lipid Parameters

Studies	Route	Study Design	Triglycerides	HDL	Cholesterol
17	10 IV 6 PO 2 D	6 RCT 11 PCT	9 No change 6 Decrease 5 IV 1 PO 1 Increase (PO)	11 No change 3 Increase 2 IV 1 PO	17 No change

The final group of studies evaluated the effect of carnitine on lipid parameters. The major outcomes measured were triglycerides, cholesterol, HDL, and LDL. LDL was reported in only a few of the studies. Ten studies used IV carnitine, six used oral, and two used dialysate delivery. There were six randomized control trials and 11 prospective clinical trials (primarily cross over design). Triglycerides showed no change in nine studies, a decrease in six studies, and an increase in one study. HDL showed no change in 11 studies and an increase in three. Cholesterol showed no change in all 17 studies. Overall, the majority of results revealed no significant changes in lipid parameters. There were no studies that directly compared carnitine therapy to conventional lipid lowering therapy.

Position Statements

American Association of Kidney Patients (AAKP)
In 1994, AAKP convened a consensus group of experts to review the available data regarding carnitine's clinical utility in renal dialysis patients.[5] The three questions were:

1. Does carnitine have a clinical role in the treatment of dialysis patients?
2. What type/types of patients should be treated with carnitine?
3. What are the proper dose and mode of administration?

The panel reviewed 42 published studies involving approximately 600 hemodialysis patients. With respect to the first question, the panel concluded that there is a definite role for carnitine in the treatment of renal dialysis patients. Concerning types of patients, the panel did not recommend routine use. Rather, the panel recommended carnitine treatment for certain conditions in dialysis patients who do not adequately respond to standard therapy: (1) muscle cramps and hypotension (2) lack of energy (3) skeletal muscle weakness and/or myopathy (4) cardiomyopathy (5) anemia or uremia unresponsive to or requiring large doses of erythropoietin. As to dosage, the panel recommended 20 mg/kg of IV carnitine after each dialysis treatment.

National Kidney Foundation

In June 2000, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (DOQI) issued a guideline for levocarnitine in maintenance dialysis patients concluding that:

- There are insufficient data to support the routine use of L-carnitine for maintenance dialysis patients.
- Although the administration of L-carnitine may improve subjective symptoms such as malaise, muscle weakness, intradialytic cramps and hypotension, and quality of life in selected maintenance dialysis patients, the totality of evidence is insufficient to recommend its routine provision for any proposed clinical disorder without prior evaluation and attempts at standard therapy.
- The most promising of proposed applications is treatment of erythropoietin-resistant anemia.
- In selected individuals who manifest the above symptoms or disorders and who have not responded adequately to standard therapies, a trial of L-carnitine may be considered.

Medicare Coverage Advisory Committee (MCAC)

Due to the complexity of the available evidence and the lack of clear consensus, this issue was sent to the MCAC. On June 20, 2001 the Drugs, Biologics, and Therapeutics Panel met to discuss the use of levocarnitine in ESRD patients. The panel was sent the CMS literature review tables, all articles contained in the CMS literature review, KDOQI guidelines, as well as information prepared by Sigma-Tau Pharmaceuticals.

During the panel meeting, twelve people spoke, representing a wide range of interests, including professional societies, physicians and other providers, Medicare contractors, pharmaceutical companies, and patients.

After much discussion and debate, the panel voted on three motions:

1. CMS should establish a mechanism to define carnitine deficiency in the ESRD patient population because there is adequate evidence that such a condition exists. The Panel voted unanimously in favor of that motion.
2. There is adequate evidence that indicates some patients benefit from levocarnitine; upon establishment of rational guidelines that identify this patient population, Medicare coverage should be provided. The Panel voted unanimously in favor of that motion.
3. There is insufficient evidence to conclude that the route of administration, be it intravenous, oral, or dialysis fluid, is an important factor in the clinical safety of L-carnitine therapy in patients with ESRD on hemodialysis. The motion carried three to one, that the evidence is insufficient.

On October 17, 2001 the MCAC Executive Committee met, discussed the merits of the three recommendations of the Drugs, Biologics and Therapeutics Panel, and ratified the recommendations. The decision was submitted to CMS on November 30, 2001.

CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, in general, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

There are three questions that need to be addressed to determine the clinical effectiveness of levocarnitine for patients on hemodialysis that develop carnitine deficiency and are symptomatic.

1. How does one define carnitine deficiency? What is the evidence that ESRD patients on hemodialysis develop carnitine deficiency?
2. What is the evidence that carnitine deficiency is involved in the pathogenesis of disease?
3. What is the evidence that the administration of levocarnitine to ESRD patients improves clinical outcomes?

There are several ways one can define carnitine deficiency. Typically, deficiency is quantified by a certain level. Ideally, we would be most interested in muscle carnitine levels but it would be impractical to require muscle biopsies as a condition for coverage. Therefore, serum carnitine levels are used. Serum levels are typically expressed as either a ratio of acylcarnitine to free carnitine, or plasma free carnitine, with the latter being the primary reporting method. Various plasma levels were used in the studies we reviewed, with most free carnitine levels averaging < 40 micromol/L. The labeling for levocarnitine states that normal plasma free levels are 40-50 micromol/L pre-dialysis.

The MCAC recommended establishing a mechanism to define carnitine deficiency. Based on a review of the scientific and clinical literature as well as the FDA-approved labeling of levocarnitine, for purposes of Medicare coverage, carnitine deficiency will be defined as a pre-dialysis (trough) plasma free carnitine level < 40 micromol/L. However, a low plasma free carnitine level is not a surrogate for adverse health outcomes in ESRD patients and, thus, does not warrant treatment unless there are clinical manifestations caused by carnitine deficiency. To address whether or not and under what circumstances the use of levocarnitine could be reasonable and necessary to treat carnitine deficiency in ESRD patients, we reviewed the scientific and clinical literature and identified five clinical conditions that theoretically could be caused by carnitine deficiency in this patient population and in whom treatment with levocarnitine theoretically could improve net health outcomes. Use of levocarnitine would be reasonable and necessary if the evidence was adequate to conclude that it is clinically effective in treating one or more of the following five conditions in ESRD patients with carnitine deficiency:

- Anemia
- Intra and interdialytic complications or symptoms
- Cardiac dysfunction
- Impaired exercise capacity and muscle strength
- Impaired lipid metabolism

The strongest body of evidence reviewed related to the effect of levocarnitine on erythropoietin-resistant anemia. Of the eleven studies reviewed (including 8 RCTs, 2 double-blind crossover trials), 5 studies reported that carnitine caused an increase or prevented a decrease in hemoglobin or hematocrit compared to placebo. Of the 5 studies that examined erythropoietin requirements, 4 studies showed a decrease in erythropoietin use after treatment with carnitine or an increase in erythropoietin requirements in the control group. In the three largest studies used to support FDA approval of erythropoeitin in ESRD patients, target maintenance hematocrits were between 30% and 36%. As a result, the evidence is adequate to conclude that the use of levocarnitine to treat ESRD patients with erythropoietin-resistant anemia (persistent hematocrit < 30% with treatment) that has not responded to standard erythropoietin dosage with iron replacement, and for which other causes have been investigated and adequately treated is clinically effective, and, therefore, reasonable and necessary.

The evidence also supports the use of levocarnitine to treat intradialytic hypotension. Intradialytic hypotension can be a significant problem in dialysis patients, occurring during up to one- third of dialysis treatments. Repeated and prolonged hypotensive episodes are known to cause significant morbidity, as well as interfere with adequate dialysis (most likely through vasoconstriction reducing perfusion of large volume areas with sequestration of solutes). Sequelae from hypotension include seizures, myocardial infarction, aspiration pneumonia, and cerebral infarctions. A systolic pressure < 110 mm Hg increases the probability of cardiac or cerebrovascular mortality. The three studies reviewed, Ahmad, Casciani and Fujita, all showed reduction in hypotensive episodes with carnitine. Although the studies were relatively small and contained methodological flaws, there was consistency and reproducibility of results, the flaws were not fatal, and the magnitude of the benefit was of moderate size. As a result, the evidence is adequate to conclude that the use of levocarnitine to treat hypotension on hemodialysis that is unresponsive to usual management and interferes with dialysis is clinically effective, and, therefore, reasonable and necessary. All the studies evaluated the effect of levocarnitine in treating recurrent episodes of hypotension. Rare or isolated episodes of hypotension generally do not require treatment other than usual management. Therefore, CMS has determined that there must be at least 2 such episodes of hypotension within a 30-day period to qualify for coverage.

The evidence is not adequate to conclude that the use of levocarnitine to treat other intra and interdialytic complications or symptoms is clinically effective. Its use for these indications is experimental, and, therefore, is not reasonable and necessary. The studies reported conflicting results, the outcomes were heterogeneous and non-specific, and some studies had important methodological flaws. Because of the various measures used, there was little consistency of results across studies. It would be helpful to have additional studies, with validated instruments, that show reproducibility using clinically-relevant outcome measures.

With respect to cardiac function, six studies examined the effect of carnitine on congestive heart failure or arrhythmias. Although it is biologically plausible that carnitine could affect cardiac muscle, studies did not demonstrate this possibility through well-designed trials. The four studies relating to the use of carnitine to improve symptoms of congestive heart failure enrolled over 140 patients, and included a randomized trial and three poorly-controlled trials. Although three of the four studies did show significant improvement in ejection fraction (EF) with the use of levocarnitine, these three studies were not adequately controlled. Therefore, it is not possible to determine if the purported increases in EF were caused by levocarnitine or other factors. The three poorly-controlled studies did show similar results in that EF increased, but the patient populations were not the same in the various studies and, therefore, conclusions about the clinical effectiveness of levocarnitine cannot be drawn across these studies. The one randomized controlled trial (Fagher 1985), however, did not show any improvements in EF.

Of the two studies that evaluated the effect of levocarnitine on arrhythmias, the one randomized controlled trial (Ahmad (1990)) showed no benefit from levocarnitine while the less rigorous study (Suzuki (1982)) showed a decrease in premature beats. The number, precise nature, and clinical significance of the arrhythmias evaluated in these studies were not clearly defined. This type of information is important in determining whether or not levocarnitine therapy improves net health outcomes, because some arrhythmias are and others are not associated with morbidity and mortality. Therefore, the evidence is not adequate to conclude that the use of levocarnitine for the treatment of cardiac dysfunction is clinically effective. Its use for this indication is experimental, and, therefore, is not reasonable and necessary.

With respect to muscle strength and exercise capacity, the studies have serious methodological flaws. As in the case of intra/interdialytic complications and symptoms, the studies used various outcome measures, making it difficult to draw conclusions across studies. For several of the outcome measures used, some studies reported positive findings while some reported negative results. Furthermore, it is uncertain that some of these measures have clinical relevance and, thus, cannot be used as surrogates to demonstrate that levocarnitine improves net health outcomes. As a consequence, the evidence is not adequate to conclude that the use of levocarnitine to improve exercise capacity or muscle strength is clinically effective. Its use for these indications is experimental, and, therefore, is not reasonable and necessary.

There is little data to support the use of levocarnitine for the treatment of any type of dyslipidemia. The majority of studies showed no significant change in lipid parameters. Moreover, there are well-established effective therapies that already exist. As a result, the evidence is not adequate to conclude that the use of levocarnitine to treat dyslipidemia is clinically effective. Its use for this indication is experimental, and, therefore, is not reasonable and necessary.

We encourage parties interested in this topic to undertake studies that will provide clear evidence of improved net health outcomes for other indications.

DECISION:

This decision memorandum announces our intention to issue a national coverage determination for the use of levocarnitine in ESRD patients. Intravenous levocarnitine will only be covered in ESRD patients who have been on dialysis for a minimum of three months for one of the following indications:

Patients must have documented carnitine deficiency, as noted by a pre-dialysis (trough) plasma free carnitine level < 40 micromol/L, along with signs and symptoms of:

1. Erythropoietin-resistant anemia (persistent hematocrit < 30% with treatment) that has not responded to standard eythropoietin dosage with iron replacement, and for which other causes have been investigated and adequately treated; or

2. Hypotension on hemodialysis that requires intervention and is unresponsive to all usual management measures (e.g., fluid management) and interferes with dialysis. Such episodes of hypotension must have occurred during at least 2 dialysis treatments in a 30-day period.

Continued use of levocarnitine will not be covered if improvement has not been demonstrated within 6 months of initiation of treatment. Most of the studies reviewed that reported a positive result found a benefit with levocarnitine within six months or less of treatment.

All other indications for levocarnitine are noncovered in the ESRD population.

For a patient currently receiving intravenous levocarnitine, Medicare will cover continued treatment if:

1. Levocarnitine has been administered to treat an indication covered under the national policy described above; and

2. The patient's medical record documents a pre-dialysis (trough) plasma free carnitine level < 40 micromol/L prior to the initiation of therapy; or

3. The treating physician certifies that in his/her judgment, if treatment with levocarnitine is discontinued, the patient's pre-dialysis carnitine level would fall below 40 micromol/L and the patient would become symptomatic from erythropoietin-resistant anemia or intradialytic hypotension.

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1 CHPP is now known as the Center for Medicare Management.

2 Note that intradialytic hypotension has been categorized under the cardiac dysfunction category in some reviews, and cardiac dysfunction can cause vascular instability during dialysis. However, other noncardiac etiologies for hypotension do exist, which includes excessive fluid removal during the dialysis procedure. In the absence of a specific examination of cardiac function, hypotension was considered under this category.

3 Actual number of hypotensive episodes increased in the control group, but this was not statistically significant.

4 Untreated or unsuccessful treatment of CHF typically results in an enlarged heart.

5 Role of L-carnitine in treating renal dialysis patients. *Dialysis and Transplantation* 1994;23:

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